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Risk factors for carbamazepine elevation and toxicity following epilepsy surgery

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Summary

Summary: A proportion of patients undergoing epilepsy surgery, and receiving carbamazepine (CBZ), experience significant elevations in CBZ plasma concentrations, some with associated CBZ toxicity. The objective of this study was to identify significant risk factors for elevations (>12 μg/ml) in CBZ concentrations and CBZ-induced toxicity following epilepsy surgery.

Methods: We retrospectively examined charts of 74 inpatients (31 children and 43 adults) chronically receiving CBZ and undergoing epilepsy surgery between January 1996 and June 2000. Patient demographics, medications, type of surgery, seizure history, adverse events, CBZ doses and concentrations were evaluated.

Results: 51.2% of adults and 51.6% of pediatric patients had drug elevations. In the pediatric group, 12.9% had symptoms of toxicity compared to 9.3% in the adult group. Five risk factors—pre-operative CBZ dose, fentanyl dose, surgery day CBZ concentration, body weight, and blood loss—were related to post-operative CBZ concentrations. Three risk factors: age <18 years, pre-operative CBZ dose, and the surgery day CBZ (immediate pre-operative) concentration, were significantly related to the outcome measure of abnormal CBZ concentration (>12 μg/ml). Two variables significantly related to toxicity were average post-operative CBZ dose and the surgery day CBZ concentration. Increases in concentrations occurred at a mean 33 ± 13.7 h (range: 11–74 h) after surgery.

Discussion: Based upon our results in patients with one or more risk factors, we suggest that reduction of post-operative CBZ doses be considered.

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Introduction

Carbamazepine (CBZ) is an anticonvulsant commonly used in the treatment of both generalized and partial-onset seizures.[1] CBZ is considered the drug of choice for patients suffering from partial seizures; as a result, CBZ is used in many epilepsy surgery patients.

CBZ is unique among anticonvulsants, in that it induces its own hepatic metabolism (i.e., autoinduction). This process occurs over the 1st month of therapy with steady state clearance rates being reached after this time. After autoinduction is complete, CBZ reaches steady-state plasma concentrations within 4 days of therapy.[1] Average therapeutic plasma concentrations of the drug range from 4 to 12 μg/ml. The drug has a relatively long half-life, with a range of 8—72 h.[1] The cytochrome P450 3A4 enzyme (CYP3A4) converts CBZ to its active metabolite, CBZ 10,11-epoxide.[1]

Investigators have noticed that some individuals who are on CBZ therapy, and who undergo epilepsy surgery, have elevations of carbamazepine serum concentrations during the post-operative period. Some individuals with elevations of drug concentrations have developed symptoms of carbamazepine toxicity. We are not aware of elevations in the concentrations of other anti-epileptic medications during the post-operative period.

Cruz-Rodriguez and others were one of the first to describe this phenomenon in a group of patients undergoing epilepsy surgery, in 1989.[2] This study evaluated 32 patients who were on CBZ therapy, and who underwent corpus callosotomy, temporal lobectomy, or subdural grid placement for seizures.[2] CBZ concentrations reached a maximum value on the 4th post-operative day.[2] Further, this elevation in CBZ concentrations was 25% higher than baseline.[2]

A case report by Wright and others described post-operative carbamazepine toxicity in a patient who underwent cardiothoracic surgery.[3] The report described a patient who had elevation of CBZ to 21.5 μg/ml on the 2nd post-operative day from pre-operative steady-state concentrations that ranged from 6.6 to 9.3 μg/ml, and who suffered symptoms of CBZ toxicity, such as lethargy, diplopia, dysarthria, and nystagmus.[3]

Gidal and others studied CBZ metabolites such as CBZ 10,11-epoxide, and the drug-binding protein, α_1-acid glycoprotein, during the pre- and post-operative period.[4] The authors concluded that CBZ and CBZ 10,11-epoxide concentrations increase during the post-operative period in some patients, but such elevation was not the result of alterations in serum drug-binding to plasma proteins.[4]

To date, no study has elucidated the cause of CBZ elevation and toxicity during the post-operative period. However, as a result of these previous studies, it is evident that a certain percentage of the population will have elevations of CBZ concentrations during the post-operative period, and some of these individuals will go on to develop symptoms of carbamazepine toxicity.

Our objective in this study was to identify risk factors for elevations in CBZ concentrations, and CBZ-induced toxicity following epilepsy surgery. In addition, we believed that fentanyl, an analgesic that is commonly administered during the intraoperative period, may be involved in CBZ elevation. It became evident from recent studies such as one by Hase, Oda and others, that fentanyl may inhibit the CYP3A family of hepatic enzymes.[5] Hase and coworkers evaluated the relation between fentanyl, and its effect on the drug midazolam, which is metabolized by CYP3A.[5] Patients who received fentanyl during the intraoperative period had higher post-operative concentrations of midazolam, compared to patients who did not receive fentanyl (placebo group).[5] Through such inhibition of the CYP3A family of enzymes, and possibly CYP3A4, fentanyl may likewise, cause an elevation of CBZ concentrations during the post-operative period by preventing CBZ metabolism.

Methods

We reviewed 336 patients who underwent some form of epilepsy surgery between January 1996 and June 2000. To be included in the study, patients had to have been on a stable dose of CBZ for greater than 1 month prior to the date of surgery. Patients who underwent subdural grid placement for mapping of seizure foci were not included in the study because these patients either had their antiepileptic medication reduced, or discontinued during the post-operative period. We found that 74 patients met these criteria, and were therefore included in our study group. Of these 74 patients, 31 were children ($<$18 years) and 43 were adults.

The mean age of the pediatric group was 10.8 years, and the median age was 12 years. The age range was from 0.25 to 17 years. Eleven out of 31 patients in the pediatric group were adolescents ($\geq$13 years of age).

Once patients were included in the study, a thorough review of the medical records was undertaken for each patient. The following demographic information was obtained: age, race (white or non-white), sex (male or female), and weight. Also evaluated were the seizure etiology and history,

the type of epilepsy, and the type of surgery that the patient underwent. The details of the intraoperative course, such as blood loss, duration of anesthesia, duration of surgery, and the total fentanyl dose administered were examined.

In addition, each patient's medication history, including medications and dosages received during the intra- and post-operative period was verified through the medication administration records. These included, but were not limited to, other anesthetic medications administered during the intraoperative period, and other medications such as other antiepileptic drugs during the post-operative period.

We evaluated the pre- and post-operative CBZ doses and CBZ concentrations. Three risk factors, pre-operative CBZ dose, post-operative CBZ dose, and fentanyl dose, were standardized to body weight (dose/body weight). Some patients did not have CBZ concentrations drawn during the immediate pre-operative period ($<$24 h prior to surgery)—in this case, these patients' last CBZ concentration prior to surgery was obtained from medical records. Patients who did not have a CBZ concentration drawn within 6 months before the date of surgery were excluded from the study. There were seven patients who were included in the study with levels that were higher than normal. None of these patients suffered from symptoms of CBZ toxicity during the pre-operative period. Post-operative CBZ concentrations were drawn on the morning after surgery, and every morning thereafter until the patient was discharged from hospital.

Finally, a thorough review of the patient's post-operative course using the physicians' orders, progress notes, and nursing records was undertaken to find patients who suffered from CBZ toxicity during this period. The exact times at which CBZ concentrations were drawn were also documented. All CBZ concentrations were at trough. All medications administered to the patient in the post-operative period were evaluated, and patients on medications known to cause interactions with CBZ were excluded. Specifically, patients who were given propoxyphene—a component of the frequently used post-operative analgesic Darvocet®—were excluded from the study.

CBZ toxicity was divided into three groups—mild, moderate, and severe. Mild toxicity was defined as nystagmus, diplopia, intention tremor, lethargy, and blurred vision. Severe CBZ toxicity was defined as altered consciousness, namely stupor and coma. Moderate toxicity was initially defined as ataxia, nausea, and vomiting. However, we were not able to differentiate nausea and vomiting resulting from the post-operative state, versus secondary to CBZ toxicity. Therefore, moderate CBZ toxicity was redefined as ataxia. Nursing notes and physician progress notes were thoroughly evaluated for symptoms of CBZ toxicity—specifically, careful attention was paid to the presence of the characteristic neurological manifestations of CBZ toxicity.

Three outcome measures were evaluated. These were abnormal CBZ concentration, post-operative CBZ concentration, and the presence of CBZ toxicity symptoms. The difference between the first two outcome measures can be viewed as being a linear versus binary one. Abnormal CBZ concentration is a binary outcome measure. The CBZ concentration was either greater than 12 μg/ml, or it was within normal limits. Post-operative CBZ concentration is a linear measure. Only the magnitude of the CBZ concentration changes during the post-operative period was taken into consideration here.

In addition, a repeated measures ANOVA was performed to evaluate which variables were associated with all CBZ measurements (including pre-operative), and to determine which variables were significantly related to the rate of CBZ change both pre- and post-operatively (by including interactions with time post-surgery). Compound symmetry covariance methods were used, and only day 0 to day 4 post-surgery were used because of sparseness of CBZ measures beyond day 4.

Risk factors were evaluated using a stepwise multivariate logistic regression for binary variables such as abnormal CBZ concentration, and presence of CBZ toxicity symptoms. Risk factors were evaluated using a stepwise multiple linear regression for the continuous variable, CBZ concentration. Significance was defined at $p < 0.05$ using two-tailed tests. Odds ratios were calculated for the increase or decrease in odds of toxicity or abnormal CBZ concentration with the risk factor at hand. Calculations were performed with SAS version 8 software (SAS Institute Inc., Cary, NC, USA).

Results

With regards to age, 42% were children, and 58% were adults; 86% of our study group was white, 14% were non-white; 45% of our study group was male, and 55% were female. Age, race, and sex were evaluated as possible risk factors. Age, race or sex was not associated significantly with any of our three outcome measures.

51.6% of the pediatric group, and 51.2% of the adult group in our study had elevated CBZ concentrations during the post-operative period. 12.9% of the pediatric group, and 9.3% of the adult group had CBZ toxicity during the post-operative period. Five patients suffered from symptoms of moderate CBZ

Table 1 Significant factors associated with post-surgery CBZ concentrations.

Risk factor	Regression estimate[a]	*p*-Value
Surgery day CBZ concentration	0.422	<0.0001
Preop CBZ dose/weight	0.178	<0.0001
Weight	0.049	<0.0001
Fentanyl dose/weight	0.145	0.02
Blood loss	−0.00292	0.03

[a] Regression estimates of effect on CBZ concentrations for each increase of 1 mcg of fentanyl/kg, 1 unit of pre-operative CBZ dose/kg, 1 unit of surgery day CBZ concentrations, 1 kg of body weight, and 1 unit of blood loss.

toxicity; three patients suffered symptoms of mild CBZ toxicity. The differences between the two groups with regards to the proportion of individuals affected were not significant for either the outcome measure of elevated CBZ concentration or CBZ toxicity. Of the seven patients with abnormally high pre-operative CBZ concentrations, six continued to have abnormally high post-operative CBZ concentrations. Two of the seven patients developed mild CBZ toxicity during the post-operative period.

The five significant factors related to post-operative CBZ concentrations were pre-operative CBZ dose (mg/kg), fentanyl dose (μg/kg), surgery day CBZ concentrations (mg/L), body weight (kg), and blood loss (ml). Increasing concentrations of all of these variables were associated with increasing CBZ concentrations, except blood loss. Increasing amounts of blood loss—approximately 100 ml up to maximal amounts of 300 ml—were related to decreasing CBZ concentrations post-operatively (Table 1).

As Table 2 shows, three risk factors were significantly related to the outcome measure of abnormal CBZ concentration (>12 μg/ml). These risk factors included age, pre-operative CBZ dose, and the surgery day CBZ concentration—the CBZ concentration on the morning of surgery. The relationship between these risk factors and this outcome measure was a very significant one (Table 2).

Table 2 Significant factors associated with abnormal CBZ > 12.

Risk factor	Odds ratio[a]	*p*-Value
Age	1.037	0.001
Pre-operative CBZ dose/weight	1.107	<0.0001
Surgery day CBZ concentrations	1.464	<0.0001

[a] Increased odds of subject having an abnormal CBZ concentration for every 1 unit increase in age (years), 1 unit increase in pre-operative CBZ dose (mg/kg), or 1 unit increase in surgery day CBZ concentration (μg/ml).

Repeated measures ANOVA was used to evaluate risk factors related to multiple CBZ measures taken from day 0 to day 4 post-surgery. Only pre-operative CBZ dose (mg/kg) ($p < 0.0001$) and day post-surgery ($p < 0.0001$) were significantly related to CBZ measures. The significance of day post-surgery indicates that, on average (±S.E.), CBZ concentrations increased 0.77 ± 0.12 μg/ml per day. There were no significant interactions with post-surgery day, indicating that there was no significant difference in the rate of CBZ change based on baseline characteristics.

The two variables significantly related to toxicity were average post-operative CBZ dose (mg/kg) and the CBZ concentration on the day of the surgery, which was measured on the morning of the surgery. The mean CBZ concentration in patients without symptoms of toxicity was 8.8 μg/ml, and 10.2 μg/ml in patients with symptoms of toxicity. CBZ toxicity was significantly related to a post-operative CBZ dose greater than 6.1 mg/kg (Table 3).

Surgery day CBZ concentration was the only significant risk factor that was related to all of the three outcome measures—post-operative CBZ concentrations, abnormal CBZ concentrations, and toxicity.

Twenty-four percent (18/74) of patients had an absolute elevation of CBZ concentration of greater than 10 μg/ml. The highest absolute increase of CBZ concentration in a patient was 13.4 μg/ml. Nine percent (7/74 patients) of patients had a reduction in their post-operative CBZ concentration from the pre-operative state. A higher pre-operative CBZ concentration was not related to a higher absolute increase in post-operative CBZ concentration. The correlation coefficient between these two variables was −0.32.

Increases in CBZ concentrations occurred at a mean of 33 ± 13.7 h after surgery, with a range of 11−74 h. CBZ toxicity occurred at a mean of 18.5 ± 13.4 h after surgery. The mean CBZ concentration at which time toxicity symptoms were noted was 12.5 ± 4.5 μg/ml, with a range of 6.2−19.6 μg/ml. Most individuals who had drug elevations during the post-operative period did so by the 3rd post-operative day, or 72 h post-operatively. The median time for the first CBZ concentration greater than

Table 3 Significant factors associated with toxicity.

Risk factor	Odds ratio[a]	*p*-Value
Surgery day CBZ concentration	1.551	0.001
Post daily dose/weight	1.193	0.005

[a] Increased odds of subject having CBZ toxicity for every 1 unit increase in surgery day CBZ concentration (μg/ml) or post-operative CBZ dose (mg/kg).

12 μg/ml was 26.5 h, and 75% of the patients who had CBZ drug elevations to the abnormal range did so by 44 h after surgery.

Discussion

A high pre-operative (surgery day) CBZ concentration was the only risk factor that directly correlated with all the three outcome measures that were evaluated. As a result, we believe that individuals who undergo epilepsy surgery should have pre-operative (surgery day) CBZ concentrations checked.

With regard to fentanyl dose, a significant ($p < 0.05$) relationship was found with increasing fentanyl dose, which correlated directly with increased post-operative CBZ concentrations. It appears that fentanyl causes inhibition of the CYP450 enzyme, especially CYP3A, as reported by Hase et al.[4] in 1997. CYP3A is also the enzyme that metabolizes CBZ. Therefore, it is possible that inhibition of the enzyme would cause decreased metabolism of CBZ. Nevertheless, this phenomenon must be further studied before recommendations regarding the use of fentanyl in the intraoperative period are made. That is, a prospective study that employs the above guidelines, and which compares the use of fentanyl to a control group, would further support such a relationship.

Increasing body weight tended to protect against CBZ elevation. We feel it is important to recognize the increased likelihood of developing CBZ elevation in people with lower body weight, especially children. Although not evaluated in our study, the ability to metabolize CBZ may be directly associated with calculated liver size based on height and weight measurements.[6]

We analyzed age as a variable independent of body weight and found it to be significantly associated with elevated post-operative CBZ concentrations >12 ug/ml. It is unclear how age is related to abnormal CBZ concentrations, but may have to do with the increased rate of metabolism of CBZ in children compared with adults.[1]

Another risk factor was decreasing amounts of blood loss, which tended to correlate with increased CBZ concentrations post-operatively. This relationship ($p = 0.03$) is not as strong as the relationship with the other risk factors, albeit a significant one. There is especially more skepticism regarding this variable and its relationship because blood loss during all of the surgeries were estimated, and some surgeries did not record blood loss, or mentioned blood loss as being ''minimal.'' Again, the impact of blood loss needs to be further examined.

Other factors that are inherent during the post-operative period include inflammatory changes, especially the release of cytokines, and other immune modulators. It is possible that these substances may alter the pharmacokinetics of CBZ during the post-operative state. However, since all patients in our study were evaluated during the post-operative state, and the duration of each surgery was taken into account—and proved to not be a significant factor in our results—it is unclear how important such substances were in the determination of CBZ concentrations during the post-operative period in our study.

We recommend that post-operative CBZ concentrations be measured every 12 h for the first 72 h of the post-operative period in patients who have one or more risk factors for CBZ elevation or toxicity because we noted that a majority of these patients developed CBZ elevation or toxicity during this time. The number of patients in this group developing either CBZ elevation or toxicity began to level off around 48 h after surgery. All other individuals with no risk factors should have CBZ concentrations checked at least every 24 h for the first 72 h of the post-operative period (Table 4).

Because of the well-established direct correlation between CBZ dose and CBZ concentration, we suggest that consideration be given to post-operative CBZ dose reduction by approximately 30% in patients who have one or more risk factors for CBZ elevation or toxicity. The reduced dose should be maintained during the initial 3—5 days after surgery. As illustrated in the above table, the median mg/kg

Table 4 CBZ pre- and post-operative doses as risk factors for CBZ elevation and toxicity.

Variable	Median[a] (all patients)	Median[a] (pediatric group)	Median[a] (adult group)
Pre-operative dose (mg/kg)	17.8	21.0	16.0
Post-operative dose (mg/kg)	17.6	18.8	16.5
Fentanyl dose (μg/kg)	4.5		
Pre-operative surgery day CBZ concentration (μg/ml)	9.25		
Body weight (kg)	67		

[a] 50th percentile of the range of pre- and post-operative doses corrected for weight.

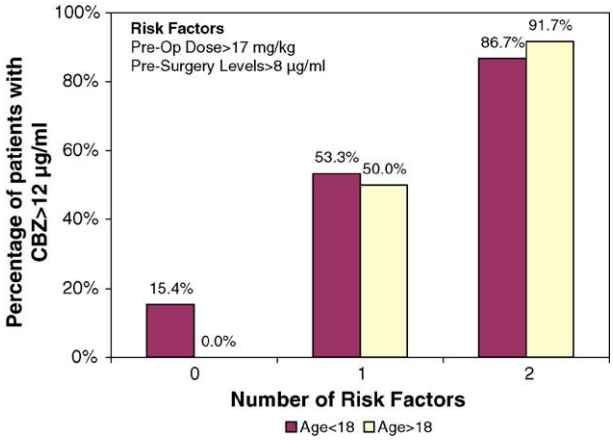

Figure 1 Percentage of patients with abnormal CBZ concentrations vs. number of risk factors.

dose in the pediatric group tended to be higher than in the adult group, therefore management guidelines must reflect the observed differences among the age groups. Specifically, we recommend that CBZ dose reduction be considered in:

- Pediatric patients with a pre-operative dose >21.0 mg/kg or a post-operative CBZ dose >18.8 mg/kg.
- Adults with a pre-operative CBZ dose >16mg/kg or a post-operative CBZ dose >16.5 mg/kg.
- All patients treated with CBZ and who have the following:
  - Fentanyl cumulative dose greater than 4.5 µg/kg.
  - Surgery day CBZ concentration >9.25 µg/ml.
  - Total body weight <67 kg.

The reduced dose should be monitored during the initial 3—5 days after surgery. Such individuals should be closely monitored, and if possible, attempts should be made to modify these risk factors (Fig. 1).

We recognize, however, that in some patients, CBZ dose reduction may lead to increased seizures. In these cases, the clinician should use appropriate clinical judgment. In this situation, if CBZ dosage is not reduced, CBZ concentrations should be monitored closely during the immediate post-operative period.

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